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(54) Title: USE OF DERIVATIVES OF TETRAHYDRO-BETA-CARBOLINES AS ANTIMETASTATIC AGENTS

(I)

(57) Abstract

The present invention concerns the use of beta-carboline derivatives of formula (I) bearing at least a free or esterified carboxylic group on the piperidine ring, for the preparation of pharmaceutical compositions having antimetastatic properties.

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USE OF DERIVATIVES OF TETRAHYDRO-BETA-CARBOLINES AS
ANTIMETASTATIC AGENTS

The present invention concerns the use of derivatives of tetrahydro-beta-carbolines for the preparation of pharmaceutical compositions having antimetastatic properties.

5 The metastasizing tumor cells are capable to migrate from the primary tumor toward the target organs by means of a mechanism which encompasses the penetration through the blood vessel walls, the entrance of the tumor cells into the blood flow, followed by the
10 successive crossing of the vessel's walls to reach the target organ.

 The penetration through the connective tissue of the vessels is accomplished by the degradation of the extracellular matrix by means of the metalloproteinases
15 released by the resident connective tissue cells, which are activated by the tumor cells. Such a mechanism, which is shared also by the not tumor tissues, is usually in a dynamic equilibrium with the connective tissue regeneration, while it is expressed in an
20 uncontrolled way in the invading cells such as the tumor or inflammatory cells and it is involved in several pathologies such as rheumatoid arthritis, osteoarthritis, septic arthritis, cornea's ulcerations, epidermic or gastric ulceration, coronary thrombosis,
25 proteinuria (WO 95/13289).

 In such processes three types of metallo-proteinases are involved: collagenases, gelatinases and stromelysins. In normal conditions their release and

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their activity are strictly controlled by endogenic proteinases-inhibitors, such as for example α_2 -macroglobulin.

Therefore, metallo-proteinase inhibitors may be
5 useful in the treatment of the pathological conditions
above described as well as of the pathological
consequences of traumas or also as contraceptive agents,
since the metallo-proteinases are involved in the
ovulation process and in the successive implant of the
10 ovule on the uterine wall. In particular, the inhibition
of the tumor metastasis by means of metallo-proteinase
inhibitors is described in Matrisian et al., PNAS USA,
83, 9413-7 (1986); Wilhelm et al., PNAS USA, 84, 6725-29
(1987); Werb et al., J. Cell Biol., 109, 872-89 (1989);
15 Liotta et al., Lab. Invest., 49, 636-49 (1983).

Metallo-proteinase inhibitors are described in US
4,511,504, US 4,568,666, US 4,771,037, WO 95/13289.

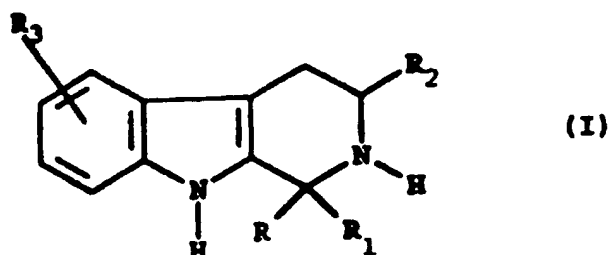
Beta-carboline derivatives are described to possess
various pharmacological activities, such as for example
20 antitumor activity [Anticancer Res., 13(6A), 2301-8
(1993); J. Antibiot., 46(11), 1672-7 (1993); EP
357.122], antiulcer activity [WO 92/04348 (19.03.92)],
antimalarial activity [J. Nat. Prod., 54(5), 1360-7
(1991)] or are described as agents that enhance the
25 absorption of antitumor drugs (JP 04275221).

None of such molecules is however described to have
antimetastatic activity.

We have surprisingly found that the tetrahydro-
beta-carbolines of formula (I) are endowed with a very
30 high activity of inhibition of the metastatic process:

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wherein:

R is selected in the group comprising hydrogen, linear or branched (C₁-C₅)alkyl, phenyl (optionally substituted with a (C₁-C₅)alkoxy group), -(CH₂)_n-COOH, wherein n is an integer from 1 to 3;

R₁ is hydrogen or a -COOR₄ group, wherein R₄ is hydrogen or (C₁-C₅)alkyl;

R₂ is hydrogen or a -COOR₄ group as above defined;

R₃ is selected in the group comprising hydrogen, halogen (chlorine, bromine, fluorine or iodine), (C₁-C₄)alkoxy, benzyloxy.

Object of the present invention is the use of the compounds of formula (I), as antimetastatic agents and as inhibitors of the tumor invasion process.

Also the enantiomers, the racemates and the diastereoisomers of the compounds of formula (I) are encompassed in the present invention, as well as their salts with pharmaceutically acceptable acids or bases.

Preferred examples of compounds of formula (I) are:

6-methoxy-1,2,3,4-tetrahydronorharmane;

1,2,3,4-tetrahydronorharman-3-carboxylic acid;

6-methoxy-1,2,3,4-tetrahydronorharman-1-carboxylic acid;

1-(4-methoxyphenyl)-1,2,3,4-tetrahydronorharman-3-carboxylic acid;

1-metil-1,2,3,4-tetrahydronorharman-3-carboxylic acid;

- 1-methyl-1,2,3,4-tetrahydronorharman-1,3-dicarboxylic acid;
- 1-(diethylmethyl)-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
- 5 (6-bromo-1,2,3,4-tetrahydronorharman-1-yl)-3-propionic acid;
- 1-isobutyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
- 1-phenyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
- 10 1-propyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
- 1-methyl-1-methoxycarbonyl-6-benzyloxy-1,2,3,4-tetrahydronorharmane;
- 1-methyl-1-methoxycarbonyl-6-methoxy-1,2,3,4-tetrahydronorharmane;
- 15 1-methyl-1-methoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydronorharmane;
- 1-methyl-1-methoxycarbonyl-6-chloro-1,2,3,4-tetrahydronorharmane;
- 1-methyl-1-methoxycarbonyl-6-bromo-1,2,3,4-tetrahydronorharmane;
- 20 1-methyl-1-methoxycarbonyl-1,2,3,4-tetrahydronorharmane.

The compounds encompassed in the present invention are known compounds and are commercially available or can be obtained by extraction from plants or synthesized according to methods reported in literature (see for example WO 92/04348).

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The compounds of the present invention have been tested in a pharmacological "in vitro" test of inhibition of MMP8 (human neutrophil collagenase). Said test provides for the determination via fluorescence of the inhibition of the degradation of a fluorescent

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substrate (DNP-Pro-Leu-Gly-Leu-Trp-Ala-D-Arg-NH₂, M1855 Bachem) by means of the catalytic domain of MMP8.

Reagents:

- 1) DNP-substrate = DNP-Pro-Leu-Gly-Leu-Trp-Ala-D-Arg-NH₂
5 (M1855 Bachem), M.W. 977.1 g/mol, concentration 25 (μM in DMSO; 2) measurement buffer = 50 mM TRIS/100 mM NaCl/10 mM CaCl₂·2H₂O, adjusted at pH 7.6 with hydrochloric acid. 3) Enzyme = catalytic domain of MMP8 (92 Kda), concentration 0.055 mg/ml in TRIS buffer.
10 Substrate and enzyme are maintained at 0°C with ice bath.

Inhibition assay:

Total volume = 1 ml of solution kept under stirring in a cuvette.

- 15 Control: 0.98 ml DMSO
0.01 ml of DNP-substrate
0.01 ml of enzyme
Assay: 0.98 ml DMSO
0.01 ml DNP-substrate
20 0.01 ml of enzyme
0.01 ml of inhibitor (10 (g/ml)).

It is measured the fluorescence at 346 nm both of the control solution (without inhibitor) and of the solution containing the inhibitor. The inhibition of the
25 catalytic activity of MMP8 results in the decrease in the DNP-substrate lysis, with related decrease in the fluorescence of the solution.

The percentage of inhibition is expressed by the following formula:

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$$\% \text{ Inhibition} = 100 - (\text{rel. unit/time}_{\text{with inhibitor}} / \text{rel. unit/time}_{\text{control}} \times 100)$$

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By repeating the experiment at different concentrations of inhibitor it is possible to determine the IC₅₀ value.

Table I shows the data of enzymatic inhibition for some representative compounds of the invention.

Table I

	compound	% Inhibition (conc. µg/ml)	IC ₅₀ (µg/ml)
10	6-methoxy-1,2,3,4-tetrahydro-norharmane	100 (0.1)	0.06
	1,2,3,4-tetrahydronorharman-3-carboxylic acid	100 (0.1)	0.07
15	6-methoxy-1,2,3,4-tetrahydro-norharman-1-carboxylic acid	100 (10)	0.05

The compounds of the present invention have also shown activity in an "in vivo" test of chemoinvasion. In the test of chemoinvasion the Costar Transwell chambers for cell culture (diameter: 6.5 mm; pore size: 8 µm) are coated with 100 µl of Type IV collagen (diluted solution 50 µg/ml, then evaporation overnight). With the same procedure the chambers are coated with a second layer of Type IV collagen (100 µl of solution at concentration 50 µg/ml). Before use, the chambers are rinsed twice with sterile water and incubated for about 1 hour at 37°C in a serum-free medium (DMEM).

The human fibrosarcoma HT1080 cells are harvested by trypsin-EDTA treatment, washed with DMEM + 10% FCS and incubated for at least 30 minutes at 37°C in the same medium. The cells are then washed with serum-free

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DMEM and resuspended in serum-free DMEM added with 0.1% BSA (fraction V), counted and diluted to obtain a final density of 3×10^5 cell/ml.

Preincubated inserts are aspirated to remove the serum-free medium. The lower compartment of the chambers is filled with 600 μ l of DMEM + 20% FCS + 1% BSA (fraction V) + compound to test. 200 μ l of cell suspension (6×10^4 cells) containing the compound to test are added to the upper compartment and the chambers are incubated at 37°C under humid atmosphere with CO₂. After first 24 hour incubation the media from both lower and upper compartments are replaced by fresh suspensions and the chambers are incubated for additional 24 hours.

Incubated filters are then washed with PBS, the cells are fixed 15 min in 4% paraformaldehyde, permeabilized in methanol (10 minutes, -20°C) and stained with May-Grunwald-Giemsa. Cells which adhere to the top of the filters are removed with a cotton swab, filters are detached from the bottom of the chambers and analyzed with microscope to determine the number of cells on the lower side of the filters.

In a control experiment in absence of metallo-proteinase inhibitor, HT1080 cells, which overexpress metallo-proteinases, are able to degrade Type IV collagen and to migrate to the lower side of the filters. In the experiment with the inhibitor however the activity of the metallo-proteinases is partially or totally inhibited and the number of cells which migrate to the lower side of the filters is decreased. The result of the experiment is expressed by the difference between the cells counted on the lower side of the

filters in the control run and in the experiment with the inhibitor.

Table II shows the data of two representative compounds of the invention.

5 Table II

	compound	chemoinvasion (conc., % inhibition)	IC ₅₀
10	6-methoxy-1,2,3,4-tetrahydro-norharmane	10 ⁻⁶ M, 61.75	0.24
	6-methoxy-1,2,3,4-tetrahydro-norharman-1-carboxylic acid	10 ⁻⁷ M, 56.5	0.2

From what it is said above it appears that the
15 compounds of the invention may be used in the treatment
of the conditions associated with the activity of the
matrix metallo-proteinases, such as rheumatoid
arthritis, osteoarthritis, septic arthritis, ulceration
of the cornea, epidermic or gastric ulcerations,
20 coronary thrombosis, proteinuria, pathological
consequences of traumas or even as contraceptive agents.

The compounds of the present invention can be
administered in doses ranging from 0.01 mg to 0.4 g per
kilogram of body weight daily. A preferred dosage
25 regimen to obtain best results is that which provides
for the use from about 1 mg to about 50 mg per kilogram
of body weight daily, employing unitary doses such as to
administer in 24 hours from about 70 mg to about 3.5 g
of the active compound to a patient having approximately
30 70 kg of body weight. Such a dosage regimen may be
adjusted to achieve the best therapeutical effect. For

example, dos s may be administered taking into account the therapeutical situation of the patient. The active compound may be administered by oral, intravenous, intramuscular or subcutaneous route.

5 The pharmaceutical compositions of the present invention contain therapeutical effective amounts of at least one compound of the invention in admixture with pharmaceutically compatible excipients.

10 Oral compositions will generally include an inert diluent or an edible carrier. They can be included in gelatin capsules or compressed into tablets. Other oral administration forms are capsules, pills, elixirs, suspensions or syrups.

15 The tablets, pills, capsules and similar compositions can contain the following ingredients (in addition to the active compound): a binder such as microcrystalline cellulose, tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, primogel, maize starch and
20 the like; a lubricant such as magnesium stearate; a fluidifier such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharine or a flavoring agent such as mint flavor, methyl salicylate or orange flavor. When the composition selected is in
25 form of capsules, it can contain in addition a liquid carrier such as a fat oil. Other compositions can contain various material which change the physical form thereof, for example coating agents (for tablets and pills) such as sugar or shellac. The material used in
30 the preparation of the compositions should be pharmaceutically pure and non toxic at the used dosages.

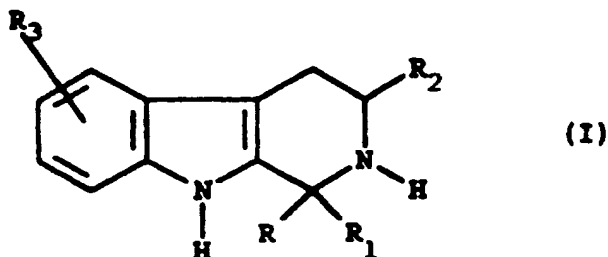
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For the preparation of pharmaceutical compositions for the parenteral administration, the active ingredient can be included in solutions or suspensions, which can comprise in addition the following components: a sterile
5 diluent such as water for injections, saline solution, oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as
10 ethylenediaminetetracetic acid; buffers such as acetates, citrates or phosphates and agents for adjusting the tonicity of the solution, such as sodium chloride or dextrose. The parenteral preparation can be included in ampoules, mono-dose syringes, glass or
15 plastic vials.

CLAIMS

1. Use of the compounds formula (I):

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wherein:

R is selected from the group consisting of hydrogen, linear or branched (C₁-C₅)alkyl, phenyl (optionally substituted with a (C₁-C₅)alkoxy group) and -(CH₂)_n-COOH, wherein n is an integer from 1 to 3;

R₁ is hydrogen or a -COOR₄ group, wherein R₄ is hydrogen or (C₁-C₅)alkyl;

R₂ is hydrogen or a -COOR₄ group as above defined;

R₃ is selected from the group consisting of hydrogen, halogen (chlorine, bromine, fluorine or iodine), (C₁-C₄)alkoxy and benzyloxy,

of enantiomers, racemates, diastereoisomers thereof and of salts thereof with pharmaceutically acceptable acids and bases, for the preparation of pharmaceutical compositions having antimetastatic activity or inhibitory activity of the tumor invasion process.

2. Use according to claim 1, in which said compounds are:

6-methoxy-1,2,3,4-tetrahydronorharmane;

1,2,3,4-tetrahydronorharman-3-carboxylic acid;

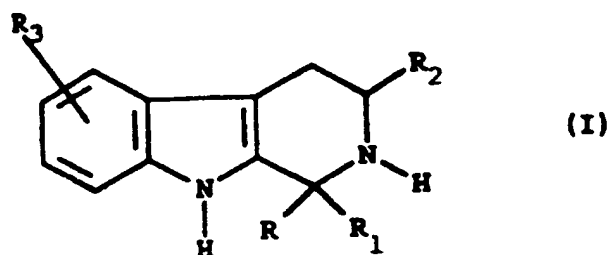
6-methoxy-1,2,3,4-tetrahydronorharman-1-carboxylic acid;

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- 1-(4-methoxyphenyl)-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
1-methyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
1-methyl-1,2,3,4-tetrahydronorharman-1,3-dicarboxylic
5 acid;
1-(diethylmethyl)-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
(6-bromo-1,2,3,4-tetrahydronorharman-1-yl)-3-propionic
acid;
10 1-isobutyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
1-phenyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
1-propyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
1-methyl-1-methoxycarbonyl-6-benzyloxy-1,2,3,4-tetrahy-
15 dronorharmane;
1-methyl-1-methoxycarbonyl-6-methoxy-1,2,3,4-tetrahydronorharmane;
1-methyl-1-methoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydronorharmane;
20 1-methyl-1-methoxycarbonyl-6-chloro-1,2,3,4-tetrahydronorharmane;
1-methyl-1-methoxycarbonyl-6-bromo-1,2,3,4-tetrahydronorharmane;
1-methyl-1-methoxycarbonyl-1,2,3,4-tetrahydronorharmane.
25 3. Use according to claim 2, in which the active compounds are:
6-methoxy-1,2,3,4-tetrahydronorharmane;
1,2,3,4-tetrahydronorharman-3-carboxylic acid;
6-methoxy-1,2,3,4-tetrahydronorharman-1-carboxylic acid.
30 4. Use of the compounds of formula (I):

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wherein:

R is selected from the group consisting of hydrogen,
 10 linear or branched (C₁-C₅)alkyl, phenyl (optionally
 substituted with a (C₁-C₅)alkoxy group) and -(CH₂)_n-
 COOH, wherein n is an integer from 1 to 3;

R₁ is hydrogen or a -COOR₄ group, wherein R₄ is hydrogen
 or (C₁-C₅)alkyl;

15 R₂ is hydrogen or a -COOR₄ group as above defined;

R₃ is selected from the group consisting of hydrogen,
 halogen (chlorine, bromine, fluorine or iodine),
 (C₁-C₄)alkoxy and benzyloxy,

20 of enantiomers, racemates, diastereoisomers thereof and
 of salts thereof with pharmaceutically acceptable acids
 and bases, for the preparation of pharmaceutical
 compositions for the prevention or the treatment of the
 conditions associated with the activity of the matrix
 metallo-proteinases.

25 5. Use according to claim 4, in which said compounds
 are:

6-methoxy-1,2,3,4-tetrahydronorharmane;

1,2,3,4-tetrahydronorharman-3-carboxylic acid;

6-methoxy-1,2,3,4-tetrahydronorharman-1-carboxylic acid;

30 1-(4-methoxyphenyl)-1,2,3,4-tetrahydronorharman-3-carbo-
 xylic acid;

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- 1-metil-1,2,3,4-tetraidronorharman-3-carboxylic acid;
1-methyl-1,2,3,4-tetrahydronorharman-1,3-dicarboxylic
acid;
1-(diethylmethyl)-1,2,3,4-tetrahydronorharman-3-carbo-
xylic acid;
(6-bromo-1,2,3,4-tetrahydronorharman-1-yl)-3-propionic
acid;
1-isobutyl-1,2,3,4-tetrahydronorharman-3-carboxylic
acid;
1-phenyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
1-propyl-1,2,3,4-tetrahydronorharman-3-carboxylic acid;
1-methyl-1-methoxycarbonyl-6-benzyloxy-1,2,3,4-tetrahy-
dronorharmane;
1-methyl-1-methoxycarbonyl-6-methoxy-1,2,3,4-tetrahydro-
norharmane;
1-methyl-1-methoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydro-
norharmane;
1-methyl-1-methoxycarbonyl-6-chloro-1,2,3,4-tetrahydro-
norharmane;
1-methyl-1-methoxycarbonyl-6-bromo-1,2,3,4-tetrahydro-
norharmane;
1-methyl-1-methoxycarbonyl-1,2,3,4-tetrahydronorharmane.
6. Use according to claim 5, in which the active
compounds are:
6-methoxy-1,2,3,4-tetrahydronorharmane;
1,2,3,4-tetrahydronorharman-3-carboxylic acid;
6-methoxy-1,2,3,4-tetrahydronorharman-1-carboxylic acid.
7. Use according to claims 4-6, in which the condition
that has to be treated is selected from the group
consisting of: rheumatoid arthritis, osteoarthritis,
septic arthritis, ulceration of the cornea, epidermic or

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gastric ulcerations, coronary thrombosis, proteinuria,
pathological consequences of traumas.

8. Use according to claims 4-6, for the prevention of
the ovulation or of the implant of the ovule on the
5 uterine wall.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/01582

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 04348 A (WARNER-LAMBERT CO) 19 March 1992 cited in the application ---	
A	WO 95 13289 A (CHIROSCIENCE LTD) 18 May 1995 cited in the application ---	
A	FR 3 395 A (ROUSSEL-UCLAF) 30 July 1963 ---	
A	ANTICANCER RES., vol. 13, no. 6a, 1993, pages 2301-2308, XP000645996 M. BELJANSKI ET AL.: "PB-100: a potent and selective inhibitor of human BCNU resistant glioblastoma cell multiplication." cited in the application ---	
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☒ Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DRUG RES., vol. 28, no. 1, 1978, pages 42-46, XP002027672 M.M. AIRAKSINEN ET AL.: "Major pharmacological effects of 6-methoxytetrahydro-beta carboline, a drug elevating the tissue 5-hydroxytryptamine level." -----</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/01582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9204348 A	19-03-92	US 5244905 A	14-09-93
		AU 9155791 A	30-03-92
		ZA 9106921 A	01-03-93

WO 9513289 A	18-05-95	AU 679286 B	26-06-97
		AU 8113394 A	29-05-95
		BR 9408025 A	17-12-96
		CN 1134705 A	30-10-96
		CZ 9601349 A	16-10-96
		EP 0728144 A	28-08-96
		FI 961976 A	09-05-96
		HU 73799 A	30-09-96
		NO 961888 A	09-05-96
		PL 314300 A	02-09-96

FR 3395 A		NONE	
